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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,191	09/15/2003	Minxue Zheng	1300-0007	9085

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,191	ZHENG ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *19-25 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2007, has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 1-39 are currently pending. Claims 19-25 and 36-39 are withdrawn as being directed to non-elected subject matter. Claims 1-18 and 26-35 are currently under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Interpretation

3. Claims 1-18 and 26-35 are product claims directed to primers and nucleic acid constructs. The claims include functional limitations and recitations of intended use that are dependent on the particular target nucleic acid sequence that the claimed primer is intended to copy or amplify. However, **no specific target sequences are specified.** Therefore, such functional limitations and recitations of intended use confer no structural limitations to the claimed primer, and will be given **no patentable weight.** As written, the claimed primer is anticipated by any prior art primer for which a target sequence exists **or could be synthesized** such that the functional limitations and intended uses recited in the claims are fulfilled. Only those limitations that impart **target-independent** structural limitations on the claimed primers will be considered. Additionally, any oligonucleotide with a 3' extendable end is a primer.

Claim Rejections - 35 USC § 112-Written Description

4. Claims 1-18 and 26-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

All claims are directed to isolated polynucleotides of one form or another which are complementary to, or substantially complementary to, or capable of being extended on an unspecified target sequence. Applicants have chosen to claim these polynucleotides not based on their chemical structure, but based on function. Since no particular sequence is specified, for either the target or the primer, this creates an incredibly large genus of potential polynucleotides covered by the claims. The claims encompass any polynucleotide for which a target sequence exists *or could be synthesized.*

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (See *Vas-Cath* at page 1117)." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (See *Vas-Cath* at page 1116)."

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. *See Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993), and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention.' Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618

> (Fed. Cir. 1989) (' [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'). Thus, an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations, not that which makes it obvious,' and by using 'such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.' Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

The written description requirement ensures that, "an applicant invented the subject matter which is claimed. Further, the written description requirement for a claimed genus may be satisfied *through a sufficient description of a representative number of species* by 1) *reduction to practice*; 2) *reduction to drawing*; or 3) *disclosure of relevant identifying characteristics (i.e., structure of other physical and/or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure* (MPEP 2163 at II(A)(3)(a)(ii)).

With regard to a representative number of species, Applicants' disclosure contains no specific sequences of targets or primers and as written the claims encompass an incredibly large genus of potential polynucleotides covered by the claims. The claims encompass any polynucleotide for which a target sequence exists *or could be synthesized.*

Since no specific polynucleotide sequence or no specific template sequence is recited, Applicants have not described the sequence information required to define the genus of all primers that would provide the requisite functional limitations required by the claims.

Therefore, as Applicants have not adequately defined the genus in terms of the structure required to perform the function and have not adequately described the enormous number of potential primers falling within the genus claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9, 12-14 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilton et al. (Human Mutation 1998, cited in the IDS).

With regard to claim 1, Wilton et al. teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see p. 253, Table 1 and col. 2 lines 10-17 and Figure 1, where Wilton et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited; see ***Claim Interpretation*** above); and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see p. 253, Table 1 and col. 2 lines 10-17 and Figure 1, where Wilton et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" is functional language which imparts no structural limitations to the claimed primer. See ***Claim Interpretation*** above).

With regard to claim 2, Wilton et al. teach the site of interest is a nucleic acid sequence (see p. 253 col. 2 under Polymerase Chain Reaction, where the target is mouse DNA).

With regard to claim 3, Wilton et al. teach the site of interest is a single nucleotide polymorphism (see p. 253 col. 1 second full paragraph and p. 254 Figure 1, where the snp is C to T *mdx* mutation).

With regard to claim 4, Wilton et al. teach the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence (see p. 254 Figure 1 and p. 253 Table 1).

With regard to claim 5, Wilton et al. teach further including a nonhybridizing spacer between the primer sequence and the blocking sequence (see p. 256, Figure 3 and legend, where the nonhybridizing sequence is the sequence which anneals back to the normal sequence therefore it does not hybridize with the target sequence carrying the mutation).

With regard to claim 9, Wilton et al. teach the spacer is nucleotidic (see p. 254 Figure 1 and p. 253 Table 1).

With regard to claim 12, Wilton et al. teach the spacer is an oligomeric segment comprised of a recurring single nucleotide (see p. 253 Table 1 SB-B(r) and SB-D(r), where the recurring single nucleotide is A).

With regard to claim 13, Wilton et al. teach the probe sequence and the spacer are separated from each other by a means for halting transcription therebetween (see p. 253 Table 1 where the primer sequence is separated from the snap back sequence by the nucleotide G, which meets the structural limitation recited in the claim because the recitation "by a means for halting transcription therebetween" is functional language).

With regard to claim 14, Wilton et al. teach the means for halting transcription is an arresting linker (see p. 253 Table 1 where the primer sequence is separated from the snap back sequence by the nucleotide G, which meets the structural limitation recited in the claim because the recitation "an arresting linker" is functional language).

With regard to claim 26, Wilton et al. teach an amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence (see p 253 under polymerase chain reaction and Figure 1 and legend).

5. Claims 1, 2 and 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Bannwarth et al. (USPN 5,573,906, 1996).

With regard to claim 1, Bannwarth et al. teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence contains a site of interest proximal to or contained within a secondary structure forming region that, in the absence of the primer, results in an unwanted secondary structure in an amplicon formed under amplification conditions so as to prevent detection of the site of interest, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see col. 2 lines 17-34 and Figure 1, where Bannwarth et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. See ***Claim Interpretation*** above); and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see col. 2 lines 17-34 and Figure 1, where Bannwarth et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" is functional language which imparts no structural limitations to the nucleic acid. See ***Claim Interpretation*** above).

With regard to claim 2, Bannwarth et al. teach the site of interest is a nucleic acid sequence (see col. 2 lines 21-23).

With regard to claim 4, Bannwarth et al. teach the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence (see Figure 1 and col. 2 lines 17-34).

With regard to claim 5, Bannwarth et al. teach further including a nonhybridizing spacer between the primer sequence and the blocking sequence (see col.2 lines 25-34, where the nonhybridizing sequence is the linker).

With regard to claim 6, Bannwarth teach the spacer is non-nucleotidic (see col. 2 lines 25-34).

With regard to claim 7, Bannwarth teach the spacer is comprised of a synthetic hydrophilic oligomer (see col. 6 lines36-52, where the linker is comprised of two propanediol groups linker by a phosphate, making it hydrophilic).

6. Claims 1 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Laibinis et al. (US 2002/0028455, March 2002).

With regard to claim 1, Laibinis et al. teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence contains a site of interest proximal to or contained within a secondary structure forming region that, in the absence of the primer, results in an unwanted secondary structure in an amplicon formed under amplification conditions so as to prevent detection of the site of interest, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see paragraphs 0010, 0040 and 0041, where Laibinis et al. clearly teach a nucleotide sequence which is complementary to a target nucleotide sequence and which has a 3' extendable end which are the only structural limitations recited. See ***Claim Interpretation*** above); and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see paragraphs 0010, 0040 and 0041, where Laibinis et al. clearly teach a nucleotide sequence which is complementary to a target nucleotide sequence and which has a 3' extendable end which are the only structural limitations recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" is functional language which imparts no structural limitations to the nucleic acid. See ***Claim Interpretation*** above).

With regard to claim 5, Laibinis et al. teach further including a nonhybridizing spacer between the primer sequence and the blocking sequence (see paragraph 0014, where the nonhybridizing sequence is the linking moiety).

With regard to claim 6, Laibinis teach the spacer is non-nucleotidic (see paragraph 0014).

With regard to claim 7, Laibinis teach the spacer is comprised of a synthetic hydrophilic oligomer (see paragraph 0014, where the linker is comprised of chains of alkylene units, specifically polyethylene gylcol, making it hydrophilic).

With regard to claim 8, Laibinis teach the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide (see paragraph 0014).

7. Claims 1, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Beattie et al. (USPN 6,268,147, 2001).

With regard to claim 1, Beattie et al. teach teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence contains a site of interest proximal

to or contained within a secondary structure forming region that, in the absence of the primer, results in an unwanted secondary structure in an amplicon formed under amplification conditions so as to prevent detection of the site of interest, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see col. 20 lines 31-66, where Beattie et al. clearly teach a teach a nucleotide sequence which is complementary to a target nucleotide sequence and which has a 3' extendable end which are the only structural limitations recited. See ***Claim Interpretation*** above); and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see col. 20 lines 31-66, where Beattie et al. clearly teach a nucleotide sequence which is complementary to a target nucleotide sequence and which has a 3' extendable end which are the only structural limitations recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" is functional language which imparts no structural limitations to the nucleic acid. See ***Claim Interpretation*** above).

With regard to claim 17, Beattie et al. teach further comprising a detectable label (see col. 20 lines 33-66 to col. 21 lines 1-37).

With regard to claim 18, Beattie et al. teach the detectable label is a radioactive isotopes (see col. 20 lines 33-66 to col. 21 lines 1-37, where ^{32}P is the label).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilton et al. (Human Mutation 1998, cited in the IDS) in view of the Stratagene Catalog (1988).

With regard to claim 27, Wilton et al. teach a dual-purpose primer according to claim 1, nucleotides appropriate to amplification of an oligonucleotide sequence, and an agent for polymerization of the nucleotides (see p. 253 col. 2 under polymerase chain reaction).

With regard to claim 28, Wilton et al. teach a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH probe such that the target nucleotide sequence is identified by the color-coding of said detecting means (see p. 253 col. 2 under polymerase chain reaction and gel fractionation and detection of bands, where the recitation of kit is not given patentable weight and the recitation of "for determining the geneotype of an individual" is an intended use recitation).

With regard to claim 29, Wilton et al. teach the detecting means is a multiplex detecting means (see p. 253 col. 2 under polymerase chain reaction and gel fractionation and detection of bands and Figure 1, where multiple alleles are detected).

With regard to claim 30, Wilton et al. teach the multiplex detecting means comprises a detectable solid substrate (see p. 253 col. 2 under polymerase chain reaction and gel fractionation and detection of bands and Figure 1, where multiple alleles are detected and the solid substrate is the polyacrylamide gel).

With regard to claim 32, Wilton et al. teach a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence in a target molecule, wherein hybridization of the blocking sequence with the second nucleotide sequence prevents secondary structure formation in the second nucleotide sequence that would otherwise interfere with hybridization of the probe sequence to the first nucleotide sequence (see p. 253, Table 1 and col. 2 lines 10-17 and Figure 1, where Wilton et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "probe" and "blocking sequence and "wherein hybridization of the blocking sequence with the second nucleotide sequence prevents secondary structure formation in the second nucleotide sequence that would otherwise interfere with hybridization of the probe sequence to the first nucleotide sequence" is functional language and imparts no structural limitation on the nucleic acid).

Wilton et al. do not teach or suggest a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dual purpose primer for amplification as taught by Wilton et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit

format saves money and resources for everyone by dramatically reducing waste. 2).. The other service provided in a kit is quality control" (page 39, column 1).

9. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bannwarth et al. (USPN 5,573,906, 1996) in view of the Stratagene Catalog (1988).

With regard to claim 28, Bannwarth et al. teach a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH probe such that the target nucleotide sequence is identified by the color-coding of said detecting means (see col. 2 lines 17-44 and Figure 1, where Bannwarth et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region to prevent formation of the unwanted secondary structure" is functional language which imparts no structural limitations to the nucleic acid).

Bannwarth et al. do not teach or suggest a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dual purpose primer for amplification as taught by Wilton et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram

amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2). The other service provided in a kit is quality control" (page 39, column 1).

10. Claim 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (USPN 6,268,147, 2001) in view of the Stratagene Catalog (1988).

With regard to claim 28, Beattie et al. teach a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH probe such that the target nucleotide sequence is identified by the color-coding of said detecting means (see example 10, where Beattie et al. clearly teach a primer sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "blocking sequence substantially complementary to a segment of the secondary structure forming region to prevent formation of the unwanted secondary structure" is functional language which imparts no structural limitations to the nucleic acid.).

With regard to claim 29, Beattie et al. teach the detecting means is a multiplex detecting means (see example 10, where multiple alleles are detected).

With regard to claim 30, Beattie et al. teach the multiplex detecting means comprises a detectable solid substrate (see example 10, where multiple alleles are detected and the solid substrate is the glass substrate for the array, or any of the substrates recited in lines 11-14 of col. 30).

With regard to claim 31, Beattie et al. teach the detectable solid substrate is a detectable microsphere (see col. 40 lines 19-28 and Figure 15 A and B).

With regard to claim 32, Beattie et al. teach a hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence in a target molecule, wherein hybridization of the blocking sequence with the second nucleotide sequence prevents secondary structure formation in the second nucleotide sequence that would otherwise interfere with hybridization of the probe sequence to the first nucleotide sequence (see col. 20 lines 31-66, where Beattie et al. clearly teach a probe sequence which is complementary to a target nucleotide sequence which is the only structural limitation recited. The recitation of "probe" and "blocking sequence and "wherein hybridization of the blocking sequence with the second nucleotide sequence prevents secondary structure formation in the second nucleotide sequence that would otherwise interfere with hybridization of the probe sequence to the first nucleotide sequence" is functional language and imparts no structural limitation on the nucleic acid).

With regard to claim 33, Beattie et al. teach further comprising a detectable label (see col. 20 lines 33-66 to col. 21 lines 1-37).

With regard to claim 34, Beattie et al. teach the detectable label is a radioactive labels (see col. 20 lines 33-66 to col. 21 lines 1-37, where ^{32}P is the label).

Beattie et al. do not teach or suggest a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dual purpose primer for amplification as taught by Wilton et al. into a

kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2). The other service provided in a kit is quality control" (page 39, column 1).

11. Claims 10, 11, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilton et al. (Human Mutation 1998) in view of Fisher (USPN 6,054,568, 2000).

The teachings of Wilton et al. are described previously.

Wilton et al. do not teach all of the limitations of claims 10, 11, 15 and 16.

With regard to claim 10, Fisher teaches the use of a non-natural base in a primer (see col. 8 lines 4-22).

With regard to claims 11, 15 and 16, Fisher teaches iso-cytosine and iso-guanine (see col. 8 lines 4-22, where iso-cytosine and iso-guanine are modified nucleosides)

One of ordinary skill in the art at the time the invention was made would have been motivated to use the non natural bases as taught by Fisher with the primer as taught by Wilton in order to improve properties such as affinity and specificity of hybridization to complementary nucleic acids. Wilton teaches the presence of the non natural base will increase specificity and affinity with respect to hybridization to complementary nucleic acids (see col. 8 lines 4-22). An ordinary practitioner would have

been motivated to use the non natural bases as taught by Fisher with the primer as taught by Wilton in order to improve affinity and specificity of hybridization of the primer in the PCR reactions used to assess the presence of single nucleotide polymorphisms.

Response to Arguments

12. Applicants' arguments filed October 8, 2007, have been fully considered but they are not persuasive.

With respect to Applicants remarks addressing statements made in the office action mailed on August 7, 2007, Applicants incorrectly characterize the statements. Firstly, Applicants assert the term "substantially complementary" is expressly defined at paragraph 0042 of the specification to mean "at least about 80 % complementarity between the nucleotides of the two strands in question" and that the assertion by the examiner that Applicants do not define the term, in the office action mailed August 7, 2007, is inaccurate. The term is not expressly defined. At least about 80 % does not expressly define "substantially complementary" because it is vague and indefinite what is meant by the phrase "at least about 80 %". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is controverted by the term "about" which implies that values above and below 80 % are permitted. Further, it is also unclear if "about 80" simply includes 78 or if it also includes 1-77 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

With respect to Applicants' remark that at the top of p. 15 of the office action mailed August 7, 2007, the examiner asserts that there is no requirement in the claims that "the target nucleic acid have any secondary structure" this remark is inaccurate as well. The statement in the office action recites "there is

no requirement in the claim that the nucleic acid sequence have secondary structure." This statement was made in reference to the claimed primer nucleic acid sequence.

Applicants argue that clause (b) of instant claim 1 represents a limitation of the primer because the limitation follows the phrase "the primer comprises." This is not the issue, the office is not asserting that the limitation of "a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" is not attributed to the primer but rather the office is arguing that this limitation imparts no structure to the primer and that this limitation is both functional and intended use language. Further the language of "a blocking sequence substantially complementary to a segment of the secondary structure forming region" refers to secondary structure found in the ***target*** not the ***primer***. Therefore the office maintains that the claimed primer is anticipated by any prior art primer for which a target sequence exists *or could be synthesized* such that the functional limitations and intended uses recited in the claims are fulfilled.

Applicants comment on p.10 of the response, that the discussion on pages 9-10 clearly shows the blocking sequence is an integral structural feature of the claimed primer. The discussion shows this feature is important to the primer, however the blocking sequence as claimed in instant claim 1 imparts no structure to the primer because as indicated above any primer for which a target sequence exists or could be synthesized such that the functional and intended use recitations of "substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest" are fulfilled.

Applicants then go on to argue, on pages 10-18 of the response, how each of the oligonucleotides in the Wilton reference, Banwarth reference, Laibinis reference and Beattie reference do not anticipate the instantly claimed primer. These arguments are directed to the functional differences of the

oligonucleotides as compared to the functional and intended use recitations of the instant claims. The structure of each of the oligonucleotides cited in each of the references is the same as the structure of the instantly claimed primer. Each of the oligonucleotides in each of the references has a 3' extendable end and is complementary to a target nucleic acid. These two structural requirements are the only structural requirements present in the instant claims. A target nucleic acid sequence exists or could be synthesized to which each of the oligonucleotdes in each of the cited references would hybridize such that the functional limitations and intended uses recited in the claims are fulfilled, therefore these arguments are not persuasive and the rejections are maintained.

Applicants' arguments with respect to the 103 (a) rejections are moot in view of the further clarification of the application of Wilton, Banwarth, Laibinis and Beattie, respectively.

Summary

13. No claims were allowable.

Correspondence

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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